Dépistage du virus de l'hépatite B dans des centres de prise en charge de personnes vivant avec le VIH en Afrique de l'Ouest

Changes in viral hepatitis B screening practices over time in West African HIV clinics

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Presentation at conferences

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Contribution of authors

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Pr Rigobert Aka Kakou contributed to designing the study and to writing the article.

Pr François Dabis, main investigator of the West African IeDEA Collaboration, contributed to designing the study and to writing the article.

Pr Gilles Wandeler contributed to designing the study and to writing the article.

Mots clés : VHB, dépistage, patients infectés par le VIH, Afrique subsaharienne

Keywords: HBV, screening, HIV-infected patients, Sub-Saharan Africa

Résumé

***Contexte*. -** Décrire les pratiques de dépistage de l'hépatite B au cours du temps chez les patients infectés par le VIH en Afrique de l'Ouest.

***Méthodes*. -** Une enquête a été menée dans les centres urbains de prise en charge du VIH en Côte d'Ivoire (3 sites), Bénin, Burkina Faso, Sénégal et Togo (1 site chacun). Parmi les patients ayant été instaurés sous traitement antirétroviral entre 2010 et 2012, 100 ont été tirés au sort chaque année dans chaque clinique. Les informations ont été recueillies à partir des dossiers médicaux. Les facteurs associés au dépistage de l'hépatite B ont été recherchés par régression logistique.

***Résultats*. -** Au total, 2 097 patients ont été inclus (âge médian de 37 ans, 65,4 % de femmes). Le dépistage de l'hépatite B a été réalisé chez 313 (14,9 %) patients, avec une augmentation au cours du temps (de 10,6 % en 2010 à 18,9 % en 2012, *P*<0,001), et une variation entre les centres. Un âge > 45 ans [rapport de cotes ajusté : 1,34 (1,01-1,77)] et une activité génératrice de revenus [rapport de cotes ajusté : 1,82 (1,09-3,03)] étaient associés au dépistage de l'hépatite B. La prévalence de l'hépatite B chronique (AgHBs+) était de 19,8 % (15,5-24,7) et 82,3 % des co-infectés étaient traités par ténofovir.

Conclusion. - Entre 2010 et 2012, le dépistage de l'hépatite B chez les patients infectés par le VIH était faible. La disponibilité croissante des tests rapides de recherche de l'AgHBs et du ténofovir devrait améliorer ce dépistage.

Abstract

***Background*. -** We aimed to describe changes in hepatitis B screening practices over a 3-year period among HIV-infected patients in West Africa.

***Methods*. -** A medical chart review was conducted in urban HIV treatment centers in Ivory Coast (3 sites), Benin, Burkina Faso, Senegal, and Togo (1 site each). Among patients who started antiretroviral treatment between 2010 and 2012, 100 per year were randomly selected from each clinic. Demographic, clinical, and laboratory data was collected using a standardized questionnaire. We assessed changes in the proportion of patients screened over time and identified predictors of screening in a multivariable logistic regression.

***Results*. -** A total of 2,097 patients were included (median age: 37 years, 65.4% of women). Overall, 313 (14.9%) patients had been screened for hepatitis B, with an increase from 10.6% in 2010 to 18.9% in 2012 (P<0.001) and substantial differences across countries. In multivariable analysis, being aged over 45 years [adjusted odds ratio: 1.34 (1.01-1.77)] and having an income-generating activity [adjusted odds ratio: 1.82 (1.09-3.03)] were associated with screening for hepatitis B infection. Overall, 62 HIV-infected patients (19.8%, 95% confidence interval: 15.5-24.7) were HBsAg-positive and 82.3% of them received a tenofovir-containing drug regimen.

***Conclusion*. -** Hepatitis B screening among HIV-infected patients was low between 2010 and 2012. The increasing availability of HBsAg rapid tests and tenofovir in first-line antiretroviral regimen should improve hepatitis B screening rates.

Introduction

At the end of 2014, the World Health Organization (WHO) estimated the number of HIV-infected people at 36.9 million [34.3-41.4] and at 2.0 million [1.9-2.2] the annual number of new infections worldwide [1]. Sub-Saharan Africa remained the most affected region, with 25.8 million [24.0–28.7] HIV-infected people and an estimated 70% of new infections [1]. Sub-Saharan Africa is also one of the most affected regions for hepatitis B virus (HBV), with more than 8% of the general population presenting with chronic HBV infection [2-4]. HBV infection is one of the main causes of cirrhosis and hepatocellular carcinoma (HCC) [5-8]. However, most patients infected with HBV are unaware of their status as routine screening for HBV in the general population is lacking [4].

As both infections share the same contamination routes (blood or sexual routes, or mother-to-child transmission), HIV-HBV co-infection is frequent, with 8-25% of HIV-infected patients who also present with chronic HBV infection in Sub-Saharan Africa [9-15]. HIV-HBV co-infected patients are at higher risk of death, poor immune reconstitution, and hepatotoxicity on antiretroviral therapy (ART) than patients only presenting with HIV infection [16-20].

WHO has been recommending since 2010 the systematic HBV screening in HIV-infected patients before ART initiation. Most national HIV/AIDS programs have now integrated this recommendation. HBV status ascertainment in HIV-infected patients is very important as it helps optimize the management of HIV-HBV co-infected patients with the initiation of a first-line ART combining at least two molecules active against both HIV and HBV, namely tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC) [21]. HBV status ascertainment in HIV-infected patients also contributes to guiding the second-line treatment choice in case of failure of the initial ART.

The prevalence of HBV among HIV-infected patients in Sub-Saharan Africa has already been measured, but the implementation of guidelines on systematic HBV screening in HIV-infected patients at initial management or ART initiation has rarely been documented. A recent study conducted in Zambia in 15 healthcare facilities of Lusaka revealed a sharp increase in

systematic HBV screening in HIV-infected patients between 2008 (1.0% of HIV-infected patients) and 2012 (46.8%) [22], with substantial differences in terms of timing of screening implementation by facility. To our knowledge, in West Africa, detailed data on HBV screening practices in HIV-infected patients and on changes in these practices over time is still lacking.

We aimed to measure the proportion of treated HIV-infected patients screened for HBV, to describe changes in HBV screening practices over time, and to assess factors associated with HBV screening in a sample of HIV clinics in West Africa.

Methods

Type of study

We performed a retrospective, multicenter study in several HIV clinics of West Africa that are part of the IeDEA Collaboration (International epidemiological DataBase to Evaluate AIDS) [23].

Study framework

We selected five French-speaking countries for the study (Benin, Burkina Faso, Ivory Coast, Senegal, and Togo). We selected a university hospital reference center for HIV management in each country. Two urban health clinics with several years of experience in HIV-infected patient management were also selected in Abidjan, Ivory Coast.

Study sample and data collection

Each year, a total of 100 individuals were randomly selected in each clinic (i.e., maximum of 300 patients per clinic) among adult HIV-infected patients (≥18 years) initiated on ART in the participating clinics between January 1, 2010 and December 31, 2012. When the number of patients initiated on ART was <100 for a given year, all patients were selected. Using a standardized questionnaire on HBV screening and management and patients' files, we collected socio-demographic, clinical, and biological data as well as data related to HBV screening practices.

Ethical consideration

This study was approved by the Ethical Committee of each of the five participating countries. Patient data was computerized using a unique code and no personal identifier was entered into the database. All patients were informed that data collected during routine visits would be collected and used for research purposes.

Statistical analyses

Quantitative variables were expressed as median and interquartile range (IQR). Qualitative variables were expressed as numbers and percentages. The univariate comparison of medians was performed using Kruskal-Wallis test, and that of frequencies using Chi-square test or Fisher's exact test depending on characteristics. The proportion of patients screened for HBV and the prevalence of HBV were calculated with their corresponding 95% confidence interval (95% CI). We used a univariable and then a multivariable logistic regression model to look for factors associated with HBV screening. Data was processed using the STATA software (StataTM 9.0 College Station, Texas, USA).

Results

Study sample

Overall, 2,097 patients were included in the study: 300 in each of the seven facilities, except for the clinic in Dakar, Senegal (n=297). Median age of patients at ART initiation was 37 years [IQR: 32-45] and median CD4 counts and alanine aminotransferase (ALAT) levels were 206 cells/mm^3 [IQR: 108-310] and 21 IU/l [IQR: 16-29], respectively. Approximately two-thirds of patients (65.4%) were women and 97.0% were only infected with HIV-1. First-line ART most often combined two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) (91.9%); 595 (28.3%) patients were initiated on TDF-based therapy: with a minimum of 13.0% in Benin and a maximum of 41.1% in Senegal.

Table I summarizes patients' characteristics at ART initiation.

Hepatitis B screening

HBV screening was performed in 313 patients (14.9%, 95% CI: 13.4-16.5), with an increase in the proportion of screening over time: 10.6% of HIV-infected patients initiated on treatment in 2010, 15.3% in 2011, and 18.9% in 2012 (*P*<0.001) (Figure 1). This proportion of HBV screening also differed by country, irrespective of the year (4.1% in Ivory Coast, 10.0% in Togo, 11.7% in Benin, 25.3% in Burkina Faso, and 45.5% in Senegal; *P*<0.001) (Figure 1). Except for Senegal and Burkina Faso where the proportion of patients screened for HBV substantially increased over the years, this proportion remained below 20% in the other countries (Figure 1). Most tested patients (86.3%) were screened before ART initiation, and the HBsAg test was the only one performed for 82.4% of patients. Patients with a positive HBsAg test were never offered an HBV viral load measurement.

Reasons for screening

Among the 313 tested patients, HBV screening was systematically performed in 201 patients (64.2%); it was performed as part of a research protocol for 29 patients (9.3%); and because of an HBV suspicion (high aminotransferase level defined by ALAT >40 IU/l) or by jaundice) in 44 patients (14.0%). Reasons for HBV screening was not mentioned in the patient's file in 12.5% of cases. Systematic HBV screening proportionally increased over the years (2.6% of all HIV-infected patients in 2010, 10.5% in 2011, and 15.7% in 2012, for all countries; *P*<0.001), while that same proportion remained stable or decreased over time for all the other reasons (Figure 2).

Prevalence of HBsAg and risk factors

Overall, 62 patients (19.8%; 95% CI [15.5-24.7]) had a positive HBsAg test. This prevalence varied by country (14.3% of tested patients in Benin, 18.5% in Senegal, 20.0% in Togo, 21.1% in Burkina Faso, and 27.0% in Ivory Coast; *P*<0.001), and by reason for screening (50.0% for high aminotransferase level, 18.7% for systematic screening, 17.2% for screening as part of a research protocol, and 17.6% for undocumented reason; *P*<0.001).

Among patients with a positive HBsAg test, 51 (82.3%) had been prescribed an ART with TDF and 3TC (or FTC). The proportion of these patients increased over time (from 55.6% in 2010 to 91.7% in 2012; *P*<0.001). Among patients with a negative HBsAg test or who were not screened for HBV, 29.2% received a TDF-based treatment. The proportion of these patients also increased over time: from 20.8% in 2010 to 39.0% in 2012.

Factors associated with HBV screening

Based on the multivariate analysis adjusted for sex, patients aged above 45 years were more likely to be screened for HBV (adjusted odds ratio [aOR]=1.34; 95% CI [1.01-1.77]) than patients aged 45 years or below. Patients with an income-generating activity were also more likely to be screened for HBV (aOR=1.82; 95% CI [1.09-3.03]) than patients without any income-generating activity. Patients for whom such information was lacking were not more often screened for HBV (Table II).

Discussion

This study is one of the first conducted in West Africa to report the proportion of HIV-infected patients screened for HBV and the changes in HBV screening practices over time. Among more than 2,000 patients treated for HIV between 2010 and 2012 in seven urban clinics of West Africa, only 313 (14.9%) were screened for HBV, even though screening practices slightly increased over the three years. We observed substantial differences between countries (a minimum of 4% in Ivory Coast and a maximum of 50% of patients in Senegal). Twenty per cent of patients who had been screened for HBV presented with a chronic HBV infection defined by a positive HBsAg test; 80% of these patients had been prescribed TDF-based ART. Patients aged above 45 years and patients with an income-generating activity were more likely to be screened for HBV than other patients.

As this study was retrospective, we could not: 1) document the prescription of an HBV screening test by physicians; this would have helped assess the proportion of HBV tests actually performed among those prescribed; 2) precisely collect important data to characterize

the profile of non-screened patients, especially data related to level of education, occupation, or level of income; 3) collect and precisely describe all reasons for screening (12.5% of missing data for this item).

Findings from our study revealed that despite a recent increase, HBV screening in treated HIV-infected patients is still uncommon in West Africa as only 19% of patients were tested in 2012. Two factors could explain this low proportion: 1) the delay, at country level, in implementing international and national guidelines on systematic screening for HBV in HIV-infected patients before ART initiation. Most study countries started implementing those guidelines in 2010 following international guidelines issuance, and a period of adjustment was probably needed for them to be widely distributed and for training healthcare professionals, as highlighted by the progressive increase in the proportion of patients screened for HBV over the years. This period of adjustment varied by country and probably resulted in the substantial differences in the results observed in the various study clinics. Conversely, the conduct of HBV prevalence studies in at least one participating clinic may have interfered with routine practices [10]; 2) as rapid diagnostic tests were not or were poorly available during the study period, HBV screening was mainly based on ELISA tests which relatively high cost was at the expense of patients. Only well off patients, including those with an income-generating activity, could thus access HBV screening as shown in our study. This subgroup of patients was indeed twice more likely to be screened for HBV than other HIV-infected patients. Rapid HBsAg detection tests have been associated with very good performances in industrialized countries [24], East and West Africa [25-28]. They are now available and most HIV-infected patients should have access to HBV screening.

We did not observe any differences in the proportion of HBV screening by CD4 count levels. Although international and national guidelines recommend the systematic screening of all HIV-infected patients regardless of their CD4 count, particular attention should be paid to patients with low CD4 count (<200 cells/mm^3) or even very low CD4 count (<50 cells/mm^3). The absence of HBV screening and adequate management in these patients could be associated

with a severe risk of hepatic decompensation due to an immune reconstitution inflammatory syndrome at ART initiation [29].

The prevalence of HBV infection (positive HBsAg test) observed in our study was 19.8%; this figure is higher than that usually reported in HIV-infected patients in West Africa (8%-15%) [9-11, 13, 30-32]. This difference could be partly explained by our conducting the study in highly specialized university hospitals that manage patients presenting with advanced HIV infection. Also, our study did not focus on serological monitoring but on collecting data related to HBV screening practices which was far from being systematically performed despite recommendations. A significant proportion of tested patients (14.0%) was thus screened for HBV because of an HBV infection suspicion. Among tested patients co-infected with HIV and HBV, 82.3% received a TDF-based ART. This prescription increased over the years and reached 91.7% in 2012. This increase highlights the progressive and marked improvement of HBV management practices.

More than five years after the publication of the first guidelines on HBV screening in HIV-infected patients, and considering the growing availability of rapid HBsAg detection tests in West Africa, changes in HBV screening in HIV-infected patients should keep on being regularly assessed as these patients should be rapidly initiated on ART [33].

Despite the slight increase in the proportion of HIV-infected patients screened for HBV between 2010 and 2012, our findings showed that HBV screening is still uncommon in West Africa and that it still varies widely by country. Involvement of health authorities and healthcare professionals, use of rapid diagnostic tests for HBV - now widely available - and use of TDF as the backbone molecule of first-line ART should help improve HBV screening and management of patients co-infected with HIV and HBV. We plan to perform the same study over the 2015-2017 period to assess practice compliance with international guidelines on screening and treatment.

Conflicts of interest

The authors report no conflict of interest.

Tableau I. Caractéristiques des patients vivant avec le VIH à la mise sous traitement antirétroviral dans cinq pays d'Afrique de l'Ouest, 2010-2012 (N = 2 097). Collaboration IeDEA West Africa.

Table I. Characteristics of HIV-infected patients at antiretroviral therapy initiation in five West African countries (N=2,097). IeDEA West Africa Collaboration.

Variables	Total N=2,097	Benin N=300	Burkina Faso N=300	Ivory Coast N=900	Senegal N=297	Togo N=300
Age (years)						
Median [IQR]	37 [32-45]	35 [30-42]	35 [30-42]	38 [33-45]	41 [35-49]	35 [30-43]
n (%) ≤45	1,626 (77.5)	249 (83.0)	253 (84.3)	684 (76.0)	195 (65.7)	245 (81.7)
n (%) >45	471 (22.5)	51 (17.0)	47 (15.7)	216 (24.0)	102 (34.3)	55 (18.3)
Sex						
Male	726 (34.6)	102 (34.0)	84 (28.0)	319 (35.4)	118 (39.7)	103 (34.3)
Female	1,371 (65.4)	198 (66.0)	216 (72.0)	581 (64.6)	179 (60.3)	197 (65.7)
Type of HIV infection (%)						
HIV-1	2,035 (97.0)	298 (99.3)	289 (96.3)	858 (95.3)	290 (97.6)	300 (100.0)
HIV-2 or HIV-1&2	62 (3.0)	2 (0.7)	11 (3.7)	42 (4.7)	7 (2.4)	0 (0.0)
Occupation						
Without any income-generating activity	164 (7.8)	26 (8.7)	9 (3.0)	67 (7.4)	62 (20.9)	0 (0.0)
With an income-generating activity	1,304 (62.2)	257 (85.7)	290 (96.7)	521 (57.9)	222 (74.7)	14 (4.7)
Not mentioned	629 (30.0)	17 (5.7)	1 (0.3)	312 (34.7)	13 (4.4)	286 (95.3)
CD4 cells/mm^3						
Median [IQR]	206 [108-310]	198 [81-316]	205 [102-321]	217 [102-326]	217 [155-280]	170 [96-249]
≤200	1,017 (48.5)	159 (53.0)	145 (48.3)	412 (45.8)	113 (38.1)	188 (62.7)
>200	1,080 (51.5)	141 (47.0)	155 (51.7)	488 (54.2)	184 (61.9)	112 (37.3)
ALAT level (IU/L)						
Median [IQR]	21 [16-29]	22 [18-35]	20 [12-28]	20 [14-30]	21 [21-22]	25 [21-33]
≤40	1,824 (87.0)	248 (82.7)	270 (90.0)	766 (85.1)	287 (96.6)	254 (84.7)
>40	272 (13.0)	52 (17.3)	30 (10.0)	134 (14.9)	10 (3.4)	46 (15.3)
Antiretroviral therapy						
2 NRTIs + 1 NNRTI	1,926 (91.9)	298 (99.3)	269 (89.7)	786 (87.3)	286 (96.3)	287 (95.7)
3 NRTIs	24 (1.1)	0 (0.0)	0 (0.0)	22 (25.4)	2 (0.7)	0 (0.0)
2 NRTIs + 1 PI	147 (7.0)	2 (0.7)	31 (10.3)	92 (10.2)	9 (3.0)	13 (4.3)
TDF-based regimen						
Yes	595 (28.4)	39 (13.0)	87 (29.0)	303 (33.7)	122 (41.1)	44 (14.7)

No	1,502 (71.6)	261 (87.0)	213 (71.0)	597 (66.3)	175 (58.9)	256 (85.3)

IQR: interquartile range
ALAT: alanine aminotransferase
NRTI: nucleoside reverse transcriptase inhibitor
NNRTI: non-nucleoside reverse transcriptase inhibitor
PI: protease inhibitor
TDF: tenofovir

Tableau II. Facteurs associés au dépistage de l'hépatite B chez les patients infectés par le VIH dans cinq pays d'Afrique de l'Ouest (N = 2 097). Collaboration IeDEA West Africa.

Table II. Factors associated with hepatitis B screening among HIV-infected patients in five West African countries (N=2,097)

			Univariate analysis			Multivariate analysis		
	N	**n (%)**	**OR**	**95% CI**	**p**	**aOR**	**95% CI**	**p**
Age								
≤45	1,626	227 (14.0)	Ref.	-	-	Ref.	-	-
>45	471	86 (18.3)	1.38	1.04-1.81	0.022	1.34	1.01-1.77	0.04
Sex								
Female	1,371	190 (13.9)	Ref.	-	-	Ref.	-	-
Male	726	123 (16.9)	1.27	0.99-1.62	0.06	1.22	0.95-1.57	0.13
Type of HIV								
HIV-1	2,035	305 (15.0)	Ref.	-	-			
HIV-2 or HIV-1&2	62	8 (12.9)	0.84	0.40-1.78	0.65			
Occupation								
Without any income-generating activity	164	18 (11.0)	Ref.	-	-	Ref.	-	-
With an income-generating activity	984	236 (18.1)	1.79	1.08-2.98	0.03	1.82	1.09-3.03	0.02
Not mentioned	629	59 (9.4)	0.84	0.48-1.47	0.54	0.84	0.48-1.47	0.55
CD4 count (/mm^3)								
>200	1,080	162 (15.0)	Ref.	-	-			
≤200	1,017	151 (14.9)	0.99	0.78-1.26	0.92			
ALAT level (IU/L)								
≤40	1,825	268 (14.7)	Ref.	-	-			
>40	272	45 (16.5)	1.15	0.81-1.63	0.42			

N: Number in each group; n (%): number and percentage of patients screened for HBV
ALAT: alanine aminotransferase
OR: odds ratio
aOR: adjusted odds ratio
95% CI: 95% confidence interval
Ref.: reference class

Figure 1. Évolution de la proportion de dépistage de l'hépatite B chez les personnes vivant avec le VIH pris en charge dans les cinq pays d'Afrique de l'Ouest de 2010 à 2012. Collaboration IeDEA West Africa.

Figure 1. Evolution of the proportion of hepatitis B screening among HIV-infected patients in five West African countries from 2010 to 2012. IeDEA West Africa Collaboration

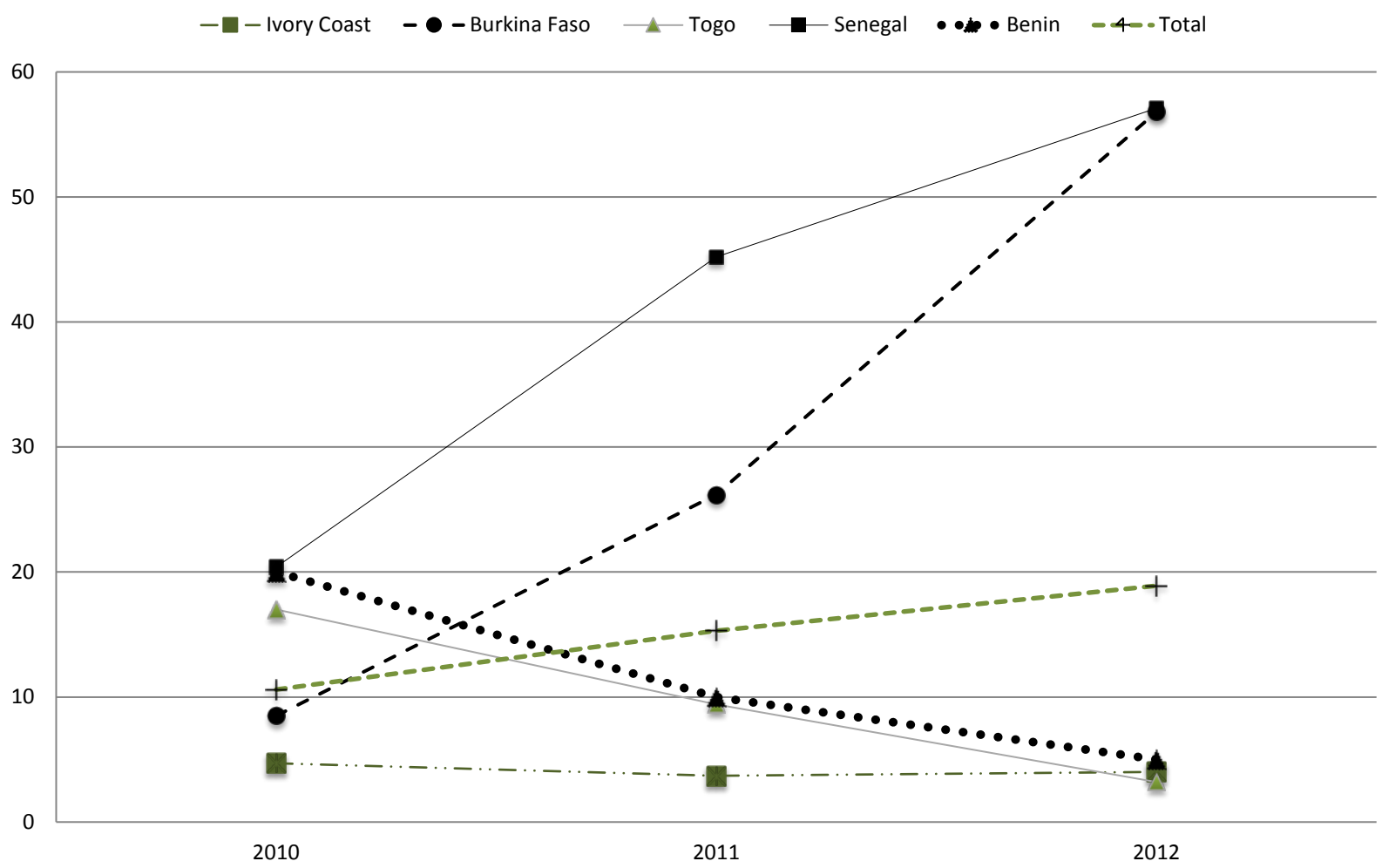
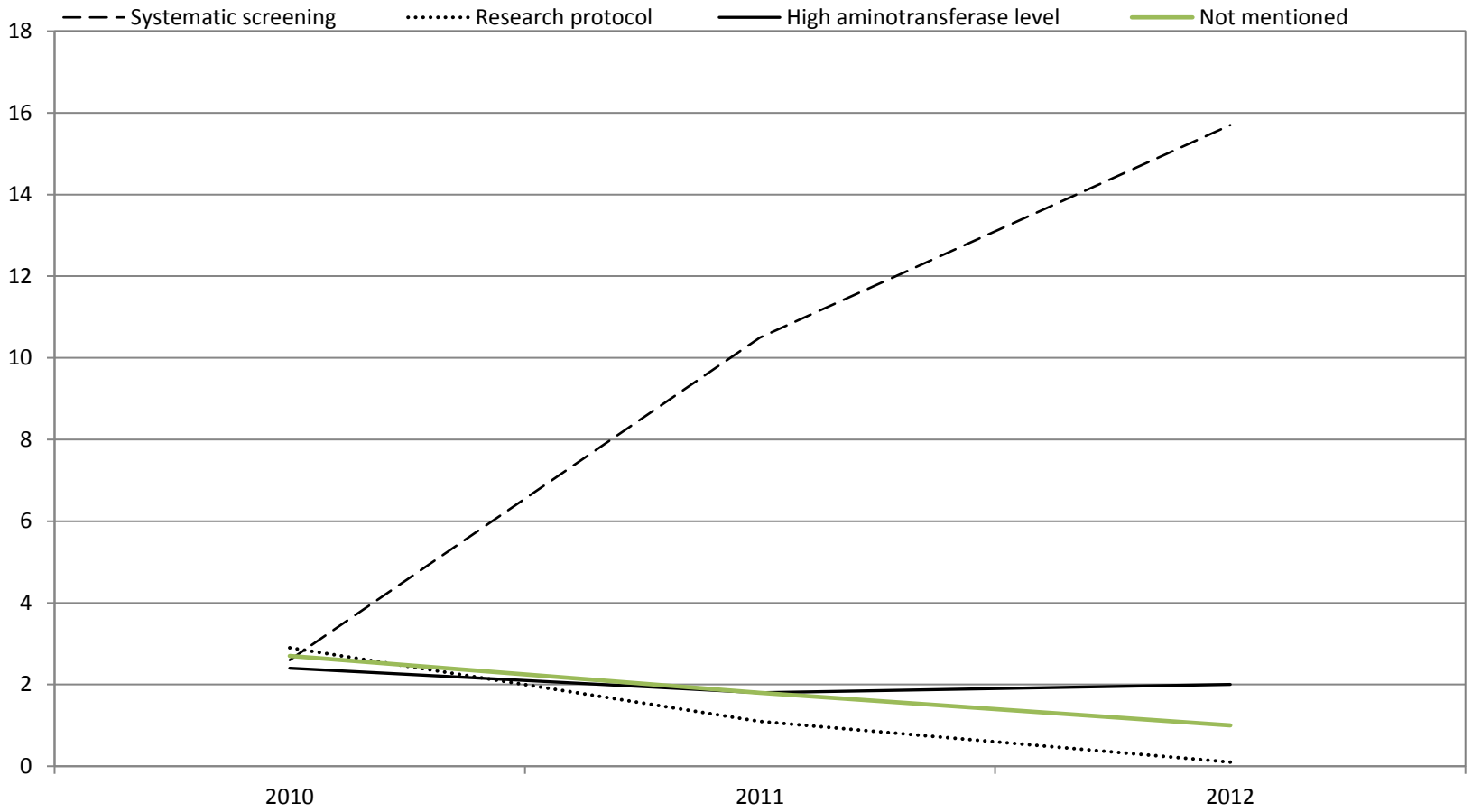

Ivory Coast
Burkina Faso
Togo
Senegal
Benin
Total
60
50
40
30
20
10
0
2010
2011
2012

Figure 2. Évolution des motifs de dépistage de l'hépatite B chez les personnes vivant avec le VIH pris en charge dans cinq pays d'Afrique de l'Ouest de 2010 à 2012. Collaboration IeDEA West Africa.

Figure 2. Evolution of reasons for hepatitis B screening among HIV-infected patients in five West African countries from 2010 to 2012. IeDEA West Africa Collaboration


Systematic screening
Research protocol
High aminotransferase level
Not mentioned
18
16
14
12
10
8
6
4
2
0
2010
2011
2012